https://doi.org/10.31925/farmacia.2022.5.1 **REVIEW**

RECOMMENDED STRATEGIES FOR *PEMPHIGUS VULGARIS* DIAGNOSIS AND MANAGEMENT IN ROMANIA

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Abstract

Pemphigus belongs to autoimmune blistering diseases and affects the skin and/or mucous membranes with a potentially fatal outcome in untreated patients. The main type is represented by *pemphigus vulgaris* (PV) which accounts for 70% of all cases in Europe. The diagnosis and management of PV in Romania are challenging due to lack of official treatment guidelines, the treatment being based on different protocols of each medical unit. This paper aims to adjust the diagnosis and management of PV in Romania according to the existing and accepted international guidelines.

Rezumat

Pemfigusul aparține grupului de boli buloase autoimune și afectează pielea și/sau mucoasele, putând avea o evoluție fatală în cazul pacienților netratați. Principala formă de boală este pemfigusul vulgar, care alcătuiește 70% din totalul cazurilor din Europa. Diagnosticul și managementul pemfigusului vulgar în România reprezintă o provocare din cauza lipsei unui protocol terapeutic oficial; tratamentul fiind bazat pe indicații diferite specifice fiecărei unități medicale. Scopul acestui manuscris este de a adapta diagnosticul și managementul pemfigusului vulgar în România în conformitate cu ghidurile existente și acceptate la nivel internațional.

Keywords: *pemphigus vulgaris*, rithuximab, guidelines

Introduction

Pemphigus represents a group of autoimmune blistering diseases affecting the skin and/or mucous membranes that may have a fatal outcome in untreated patients [19]. The classification of pemphigus includes multiple variants, the main types being *pemphigus vulgaris* (PV) - the most frequent type - and *pemphigus foliaceus* (PF). Non-classical forms include paraneoplastic pemphigus, *pemphigus herpetiformis* and IgA pemphigus. PV is the most frequently encountered type, representing 70% of all cases in Europe [30]. The evolution of this condition is chronic and patients' quality of life is significantly impaired. Its etiology is not fully understood, but autoantibodies against desmoglein 1 (Dsg-1) and desmoglein 3 (Dsg-3) play an important role in the pathogenesis. Desmogleins are proteins of epidermal desmosomes which function as adhesive structures for nearby keratinocytes. As a result, the intraepidermal adhesion is compromised in pemphigus with acantholysis leading to the development of vesicles, blisters and erosions [5]. PV may be diagnosed at any age, but usually it occurs between 40 and 60 years of age, with only few of patients being younger than 18 years old [30].

Materials and Methods

Materials

European guidelines on the management of PV and PF have recently been published [19], but in Romania official treatment guidelines do not exist, the treatment being based on different protocols of each medical unit. Moreover specific investigations (direct immunofluorescence, indirect immunofluorescence, antibody serology) are available only in university medical centres. An extensive literature search was conducted in order to accumulate evidence-based data on *pemphigus vulgaris.* Appropriate literature was achieved from three computerised bibliographical databases: PubMed, EMBASE and the Cochrane Library. The aim of this paper is to adjust the diagnosis and management of PV, according to the existing conditions in Romania.

Results and Discussion

Pathopysiology

The pathopysiology of PV consists of abberant immune responses leading to autoreactive CD4+ T helper (Th) cells, CD8+ T cells and production of autoantibodies by B lymphocytes [31]. The interaction between antigen presenting cells (APC) carrying desmoglein peptides and autoreactive T cells through HLA II molecules triggers IL-10 secretion and B cell activation with autoantibodies generation [31]. Some autoantibodies against desmoglein (Dsg) are not pathogenic and hence do not correlate with disease activity [1]. In the acute phase of PV, IgG4 against Dsg are frequently found, in contrast with IgG1 that are found in remission periods. The clinical aspects are influenced by the type of circulating autoantibodies. Skin lesions occur when both autoantibodies against Dsg-1 and Dsg-3 are present because the dysfunction of either Dsg-1 or Dsg-3 is compensated by the presence of the other. Mucosal lesions appear only in the presence of autoantibodies against Dsg-3 [30]. Genetic predisposition plays an important role in the pathogenesis of PV. HLA-DRB1*04 and HLA-A*10 genes have been detected in Ashkenazi Jewish patients with PV. Furthermore, the ST18 gene, which encodes a proapoptotic molecule, has been found among Jewish and Egyptian population [22, 30]. A Brazilian study which included 51 patients with PV showed the association of DRB1*04:02, DQB1*05:03 and HLA-B*57 genes with the development of the disease [14]. Numerous trigger factors have been described in the literature, with drugs being the most common cause. These drugs include d-penicillamine, captopril, lisinopril, candesartan, penicillin, rifampicin, carbamazepine, nifedipine, ceftazidime, hydroxychloroquine, phenobarbital, etc. Other reported trigger factors are diseases such as infections, cancers and autoimmune conditions, radiotherapy, pregnancy, stress, UV-radiation, trauma and exposure to pesticides [11, 16]. Besides, contact pemphigus is a term that refers to cases of pemphigus occurring after a contact with a variety of chemical substances [11].

Epidemiology

Pemphigus has a possible ethnic distribution (people of Mediterranean origin).

There are few data from Romania showing, through a study from the North-western region of Romania conducted during the period 2001 - 2007, an incidence of PV of 4 (95% CI: 1.088 - 10.240) and prevalence of 24.8 (95% CI: 16.045 - 36.604) *per* 1.000.000 inhabitants [3].

More recent epidemiological data of PV from Romania, between 2017 and 2019, report a relatively constant number of cases per year, *i.e.* 243 new cases in 2017 and 2019 and 275 cases in 2018. Gender distribution showed 61.5% cases in female patients and 38.5% cases in male patients. Overall prevalence was higher in urban areas (54.9%). The highest prevalence of PV cases was among patients within the age range 60 - 69 years old, while the lowest prevalence of PV cases was found within the age range 0 - 19 years old [28].

Considering the tendency for increasing incidence of autoimmune blistering diseases worldwide, further local studies need to be performed in that direction.

Clinical manifestations

Of all types of pemphigus, PV represents the most common and severe form, which affects both skin and mucous membranes [12]. The clinical aspects correlate with the presence of circulating autoantibodies. In mucosal dominant variant exclusively anti-Dsg3 autoantibodies are involved, while in cutaneous dominant variant only anti-Dsg1 autoantibodies are present. The muco-cutaneous form is the most frequent form and is characterized by the presence of both anti-Dsg1 and anti-Dsg3 autoantibodies [18]. The intra-epidermal detachment leads to the formation of flaccid and fragile blisters that may rupture easily, resulting in erosions and crusts. They develop commonly on the face, scalp, axilla, trunk or groin and leave hypo- or hyperpigmentation without scars [26]. Blisters are rarely pruritic, painful and vary in size, presenting as large vesicles (< 5 mm in diameter) or as bullae (> 5 mm in diameter) [7]. When applying pressure on the blister's wall, the lesion spreads into the nearby normal tegument (Nikolsky II sign), being a useful tool in the differentiation of PV from sub-epidermal bullous conditions [29]. The mucosal lesions involve stratified epithelium such as oral, pharyngeal, laryngeal, oesophageal, nasal, conjunctival, anal and genital mucosae [7]. Oral mucosa is affected in a majority of patients, being the onset site of PV manifestation in 50 - 75% of cases [9, 24]. Patients present with vesicles that rupture easily leading to erosions and rarely ulcers. Moreover, the erosions and ulcers represent routes of entry for a variety of

pathogenes and determine secondary infections and even sepsis [17].

The pain is the main complaint and impairs the quality of life drastically, which is assessed with the use of The Dermatology Life Quality Index (DLQI) [21]. Today there are also two tools developed specifically to determine quality of life in patients with autoimmune blistering disorders and those are Autoimmune Bullous Disease Quality of Life Questionnaire (ABQOL) and Treatment Autoimmune Bullous Disease Quality of Life Questionnaire (TABQOL), which are helpful in current practice [21].

In order to evaluate disease severity two objective scores have been developed: the Pemphigus Disease Area Index (PDAI) and the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS). PDAI rates both total activity and total damage score of skin and mucosal manifestations with a total maximum score of 263 points and divides the disease into three categories (moderate, significant and extensive pemphigus) [6].

Diagnosis

Diagnosis of *pemphigus vulgaris* includes several aspects, both clinical and paraclinical. Medical history is important in order to determine additional symptoms such as pain and pruritus, treatment contraindications or possible potential complications. Medical history needs to be documented, giving special attention to drugs that may induce PV (cephalosporins, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors and D-penicillamine) [15, 27].

Physical examination consists of evaluation of the skin and mucosal lesions with the use of PDAI and ABSIS scores [27]. Mild PV is defined by a PDAI score under 15 points; it could also be identified as lesions that involve less than 5% of the total body surface together with painless mucosal lesions that allow food ingestion without difficulties. Moderate PV is defined by a PDAI score between 15 and 45 points and severe PV is defined by a PDAI score higher than 45 points. Both moderate and severe PV are accompanied by painful cutaneous lesions that cover more than 5% of the total body surface or multiple mucosal lesions or oral mucosa lesions with impairment of food intake or weight loss [19]. Control of disease is achieved when the existing lesions start to cure and no new lesions appear. Uncontrolled disease is defined by persistent lesions and the continuous appearance of new lesions. Disease relapse is defined by the occurrence of minimum 3 additional lesions during one month which do not cease in one week or by spreading of any existing lesions after patients have achieved control of the disease (Cd) [27].

The recommandation of European Academy of Dermatology and Venereology Guidelines 2020 as criteria for the diagnosis of PV includes clinical evaluation, histopathology, direct immunofluorescence examinations and serological tests, *i.e.* anti-Dsg 1 and anti-Dsg 3 as well as indirect immunofluorescence [19].

The skin biopsy for histopathology needs to be performed from a recent blistering lesion, including its edge, where the level of split is most likely to be found. If there is a lack of blisters, the edge of an erosion may be biopsied. Both punch biopsy and ellipse incisional biopsy are performed, but the later method helps the pathologist to orientate the specimen easily [8].

PV specimens are characterized by acantholysis of the keratinocytes with suprabasal blistering. The aspect described as a "row of tombstones" is the consequence of this phenomenon [26].

Direct immunofluorescence (DIF) microscopy requires skin biopsy from clear perilesional skin or mucosa and highlights granular or linear deposits of IgG and/or C3 on the keratinocytes surface, *i.e.* inter-cellular deposition [19].

Serology includes indirect immunofluorescence (IIF) microscopy and detection of circulating autoanti-bodies by enzyme linked immuno sorbent assay (ELISA). IIF is performed on monkey oesophagus substrate or using cells that recombinantly express Dsg-1 and Dsg-3 on the cell surface (Biochip; Euroimmun). In most cases the titres of anti Dsg-1 and anti Dsg-3 autoantibodies are associated with disease activity. More than 95% of patients with PV have IgG anti-Dsg [19]. In Romania DIF and serology are performed in private medical services or in public hospitals by paying an extra fee.

A positive diagnosis of PV according to the European Academy of Dermatology and Venereology Guidelines 2020 is based on consistent clinical manifestations, histopathology, ELISA, DIF and IIF. In the case of a negative DIF, the guideline recommends a second skin biopsy for DIF examination. For the situations which do not permit another biopsy or when the second biopsy is again negative, the diagnostic algorithm comprises two methods: (1) compatible clinical manifestations with acantholysis on histological examination and positive IIF; (2) compatible clinical manifestations, histopathology examination and positive ELISA (Figure 1) [19].

Based on this European diagnostic guideline, in Romania it is possible to encounter cases which need additional fees in order to establish a positive diagnosis of PV. At present, in Romania, not all cases are diagnosed consistent with the European guide-lines 2020, which can lead to negative consequences by using unjustified medicines for patients such as high dose long-term corticosteroid therapy. It results in high costs for the treatment of the primary disease, as well as for the additional treatment in patients initially treated ineffective.

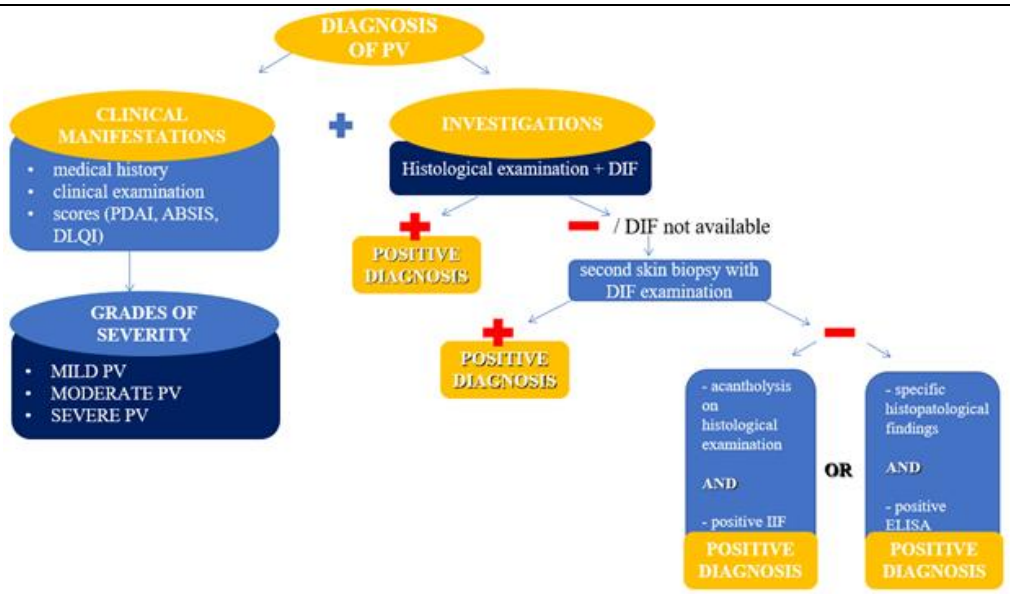

Figure 1.
Diagnostic algorithm for PV

Therapeutic approach

The management of PV includes different therapeutic options depending on its severity. Along therapy, several phases are described.

The consolidation phase finishes when no more additional clinical lesions appear in the last two weeks of treatment and the existing lesions recovered 80% and represents the moment when the dose of corticosteroids may be reduced [27].

A complete remission on therapy is defined as the absence of new or established lesions while the patient is receiving minimal therapy. A complete remission off therapy is defined as the absence of new and/or established lesions while the patient is off all systemic therapy for at least two months. Minimal therapy is defined as less than, or equal to, 10 mg/day of prednisone (or the equivalent) and/ or minimal adjuvant therapy for at least two months [27].

Mild PV

The first-line therapy is represented by the administration of corticotherapy only (prednisone 0.5 - 1.0 mg/kg *per* day) or in association with azathioprine 2 mg/kg *per* day, mycophenolate mofetil 2 g/day or mycophenolate sodium 1440 mg/day. In the first-line therapy, the guideline also recommends rituximab (1 g at week 0 and 1 g at week 2) as single treatment or associated with oral corticotherapy (prednisone 0.5 mg/kg/day), which shall be reduced rapidly and then stopped within 3 to 4 months. The second line therapy is considered in patients with stubborn lesions and/or adverse reactions to corticotherapy or contraindications to immunosuppressive agents. For the category of patients treated in the beginning with corticosteroids only, the recommendation is to add rituximab (1 g at week 0 and 1 g at week 2), followed by reduction in the dose of prednisone/prednisolone with subsequent cessation. On the other hand, for the category of patients treated at first with rituximab and corticosteroids, the aim is to major the dose of prednisone/ prednisolone up to 1 mg/kg/day (Figure 2) [19].

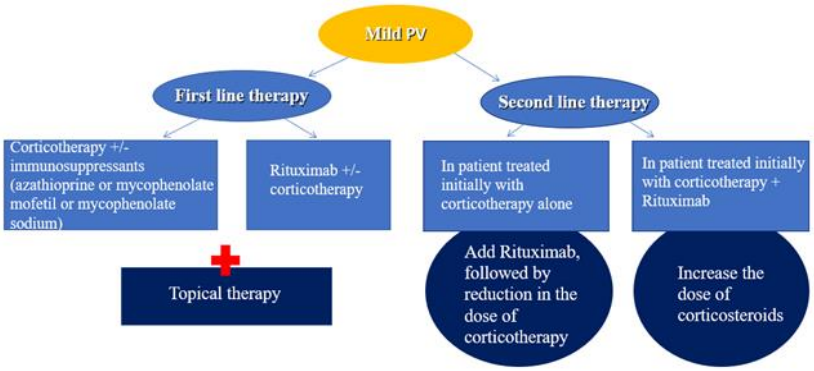

Figure 2.
Therapeutic algorithm of mild PV – Second line

Moderate to severe PV

In moderate to severe PV treatment recommendations consist of first-line and second-line therapy. First line-treatment includes rituximab (1 g at week 0 and 1 g at week 2) in association with systemic corticotherapy (prednisone 1 mg/kg/day), with gradual decreasing of dose until cessation of steroids within 6 months. If systemic corticotherapy is contraindicated, rituximab may be used as single treatment or together with topical corticosteroids. Systemic corticosteroids represent an alternative first-line treatment when rituximab is unavailable or contraindicated. An initial dose of 1 - 1.5 mg/kg/day of prednisone is administered as monotherapy or in association with azathioprine 1 - 2.5 mg/kg/day, mycophenolate sodium 1440 mg/day or mycophenolate mofetil 2 g/day. In case of failure to achieve disease control at week 3 - 4 in patients treated initially with rituximab plus prednisone, then an increase of prednisone dose (1.5 mg/kg/day) or i.v. pulses of corticosteroids may be considered. For patients treated at first with 1 mg/kg/day of prednisone as monotherapy, the next step is to administer rituximab (1 g at week 0 and 1 g at week 2) and to level up the dose of prednisone to 1.5 mg/kg/day. An alternative choice is to add azathioprine 1 - 2.5 mg/kg/day, mycophenolate sodium 1440 mg/day or mycophenolate mofetil 2 g/day. For patients treated at first with 1.5 mg/kg/day of prednisone alone, the guideline recommendations suggest to introduce either rituximab (1 g at week 0 and 1 g at week 2) or azathioprine 1 - 2.5 mg/kg *per* day, mycophenolate sodium 1440 mg/day or mycophenolate mofetil 2 g/day (Figure 3) [19].

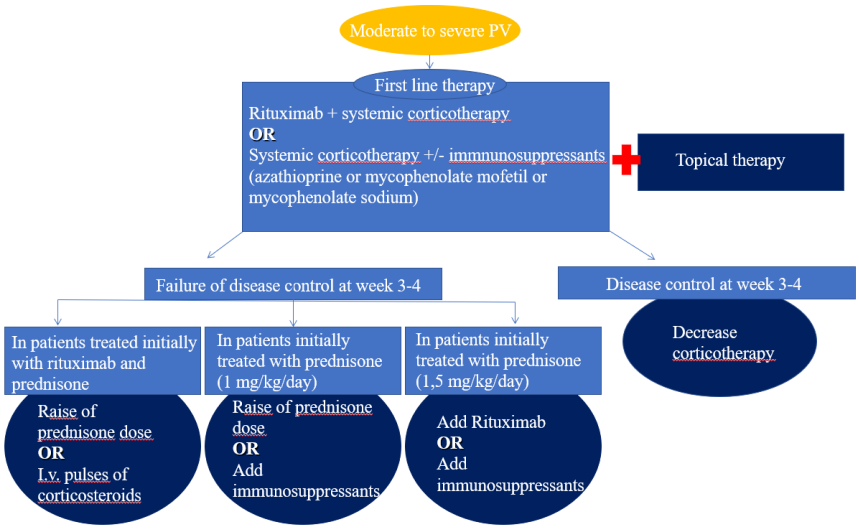

Figure 3.
Therapeutic algorithm of moderate to severe PV

In moderate to severe PV cases an assessment at six months after the first cycle of rituximab is necessary. In patients with severe PV at first presentation and/or high level of anti-Dsg antibodies after 3 months of therapy in which the remission was complete, it may be recommended to administer an additional dose of rituximab (500 mg or 1 g) at month 6 following rituximab treatment. If the complete remission was not achieved, rituximab (1 g at week 0 and 1 g at week 2) could be considered [19].

In patients who achieved complete remission, one dose of 500 mg of Rituximab should be administered at month 12 and another dose of 500 mg of Rituximab at month 18, especially when anti-Dsg antibodies are detected in high titres [19].

Uncontrolled disease

If the disease is not controlled after 3 - 4 weeks, the treatment should be reconsidered.

In patients firstly treated with both prednisone and rituximab it is recommended to level up the dose of prednisone to 1.5 mg/kg/day or to administer pulses of methylprednisolone 0.5 - 1 g/day or dexamethasone 100 mg/day, for three successive days [19].

In patients with first-line therapy consisting of corticosteroides (prednisone 1 mg/kg/day) only it is advised to include rituximab (1 g at week 0 and 1 g at week 2) or immunosuppressant agents such as azathioprine 1 - 2.5 mg/kg/day, mycophenolate mofetil 2 g/day, mycophenolate sodium 1440 mg/day if rituximab is not available and to level up the prednisone dose to 1.5 mg/kg/day [19] .

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There are three treatment options for *pemphigus vulgaris* refractory at previous therapy lines: intravenous immunoglobulins (2 g/kg/cycle across 2 - 5 successive days, monthly); pulses of methylprednisolone (0.5 - 1 g/day) or dexamethasone (100 mg/day), for three successive days; immunoadsorption (≥ 2 cycles across 3 - 4 successive days, monthly) [19].

In order to receive rituximab therapy in Romania, the patients need to pay for the medicine and the costs are not supported by the National Health Insurance House of Romania. In consequence many patients apply for this treatment abroad. In Romania approved rituximab agents are Mabthera (original) and biosimilars (Blitzima, Rixathon, Ruxience and Truxima) [2].

Supportive care

The cutaneous and mucosal lesions may be additionally treated with topical corticosteroids or intralesional corticotherapy, after antiseptic baths. Analgesics may be required by painful lesions. Dental hygiene is of great importance [19].

Vaccination

The patients who are treated with rituximab and immunosuppressants are not allowed to receive live vaccines [19].

The seasonal influenza vaccine belongs in the category of inactivated vaccines and is allowed in PV patients on rituximab and immunosuppressant agents, because the vaccine associated risks are lower than the consequences to contract influenza. It is advised to administer influenza vaccine 4 weeks before the initiation of rituximab therapy or for the patients who are already on rituximab therapy, the vaccination should be done 12 - 20 weeks after completing one cycle of rituximab [32].

Up to the present, there are scarce data about COVID-19 vaccination in PV patients. The current consensus is in favour of COVID-19 vaccination, but one must consider that flares may appear secondary to it. Nevertheless, the flares don't contraindicate immunization and should be treated accordingly [10].

Relapse therapy

For patients who received rituximab and corticosteroids the relapse treatment consists of: (*i*) when relapse occurs during dose reduction of prednisone in the first 4 months, the indication is to raise the dose of systemic corticosteroids [19]; (*ii*) when relapse appears during the dose reduction of prednisone from month 4 to month 6 it is advised to perform a cycle of rituximab (2 g). The administration of rituximab at month 6 as maintenance therapy is not recommended anymore in this situation [19]; (*iii*) when there is a relapse once therapy with prednisone is finished, there are no current recommendations [19].

For patients who received systemic corticosteroids only, the relapse treatment consists of: (*i*) when the relapse appears during the dose reduction of prednisone it is indicated to add rituximab (1 g at week 0 and 1 g at week 2) [19]; (*ii*) if rituximab is not accessible or is contraindicated, the dose of corticosteroids should be increased and immunosuppressive therapy such as azathioprine (1 - 2.5 mg/kg/day), mycophenolate mofetil (2 g/day), or mycophenolate sodium (1440 mg/day) needs to be associated [19].

Monitoring of PV patients

Before initiation of rituximab therapy it is advised to screen for hepatitis B infection (HbsAg – status and HbcAb – status) and for tuberculosis (Quantiferon, X-ray), due to the national situation with high incidence of tuberculosis [25]. In patients with positive hepatitis B serology or Quantiferon test the collaboration with the hepatologist and pneumologyst respectively is necessary in order to establish the treatment and to prevent reactivation of hepatitis B or tuberculosis [23].

After starting the corticosteroid therapy, the patient should be evaluated at intervals of two weeks. Once the disease is controlled, the consolidation phase begins while the patient should be assessed at two weeks in order to establish when to taper the dose of corticosteroids. In the period when the corticosteroid dose is gradually reduced, the follow-up is every month, three successive months. When the patient reaches complete remission on therapy, the monitoring is recommended every three months (Figure 4) [19].

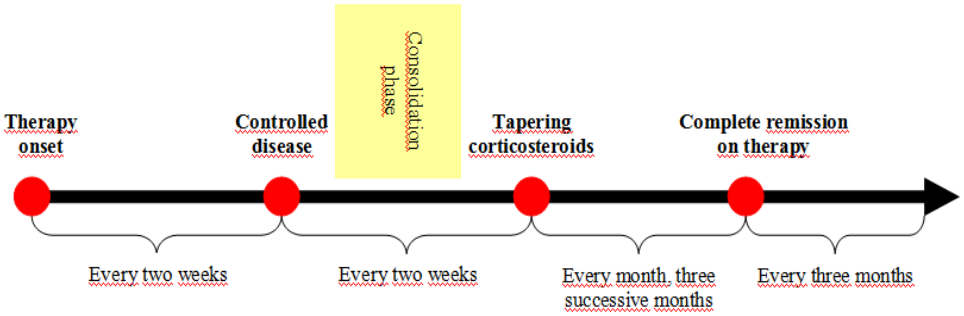

Figure 4.
Monitoring of PV patients

Predictive factors for overall mortality and relapse

The risk factors identified for overall mortality and relapse have major implications for the stratification of patients and design of personalized therapeutic plans. An age of onset ≥ 65 years, presence of coronary heart disease, cardiac arrhythmia, a level of anti-Dsg1 autoantibodies ≥ 100 U/mL and erythrocyte sedimentation rate (ESR) ≥ 30 mm/h, at diagnosis was associated with poor survival [4].

Additionally, a body surface area (BSA) involvement ≥ 15% at diagnosis and failure to achieve auto-antibody titre negativity in clinical remission were shown to be a significant predictors of relapse [13].

Conclusions

A specific care strategy for patients with PV may be performed by dermatologists based on these recommendations regarding diagnosis and treatment. With the help of the European Academy of Dermatology and Venereology Guidelines 2020 an updated treatment strategy is possible.

To improve the diagnosis of PV we suggest IFD and serology investigations among the diagnosis methods supported by the National Health Insurance House of Romania. These methods could be provided in new structures dedicated to the management of autoimmune bullous diseases. In addition, we propose that rituximab therapy should urgently be available free of charge in Romania since this drug has been approved by the European Medicine Agency in 2019 for treatment of moderate to severe PV based on the results of the Ritux 3 trial and confirmed by the Pemphix trial.

Conflict of interest

The authors declare no conflict of interest.

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